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10/526,062	11/14/2005	Ralph Biemans	VB60394	5458

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GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, MAI B482
FIVE MOORE DR., PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
08/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USCIPRTP@GSK.COM
LAURA.M.MCCULLEN@GSK.COM
JULIE.D.MCFALLS@GSK.COM

Office Action Summary	Application No.	Applicant(s)	
	10/526,062	BIEMANS ET AL.	
	Examiner	Art Unit	
	SAMUEL W. LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50 and 52-63* is/are pending in the application.

4a) Of the above claim(s) *1-24,37-50 and 52-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/28/05* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-50 and 52-63 are pending.

The amendment filed 5/8/08 which amends claims 6, 50 and 59, and cancels claim 51 has been entered.

Priority

Applicant's claim for foreign priority under 35 U.S.C. 119 (a)-(d) based United Kingdom patent application 0220199.4 filed 8/30/2002 is acknowledged.

Election/Restrictions

The Applicants' election (filed 5/8/08) of Group 3, claims 25-35 and 36 with traverse is acknowledged. The traversal is on the ground(s) that since claim 37 product is produced by the method of elected Group 3, claim 37 and claims 38-50 (the composition thereof) which depend from claim 37 should be rejoined with the claims of Group 3 (the bridging pages 11-12, and page 13).

The applicants' arguments are found unpersuasive because the product (Group 3, claims 25-35 and 36) and the process (including claims 37-50) of making said product are considered to be distinct inventions, because the isolated and refolded FrpB protein of claim 37 and the dependent claims therefrom can be made by another and materially different process (MPEP § 806.05(f)); e.g., by biosynthesized through cell-free in vitro translation followed by conjugated in situ refolding via engineered molecular chaperone. Thus, the product claims 37-50 will not rejoined in this case herein with the elected process claims 25-36 (for the rejoinder practice in accordance with the provisions of MPEP § 821.04, please see the Office action mailed 3/21/08,

pages 5-6). Therefore, the requirement is therefore still deemed proper and is therefore made FINAL.

Claims 1-24, 37-50 and 52-63 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 25-36 are under examination.

IDS

The reference cited in the IDS filed 2/28/05 has been considered by Examiner.

Objection to specification

The disclosure is objected to because of the following informalities:

(1) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code in page 16, line 20. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Applicants may remove "http://" so that the hyperlinker becomes inactive, i.e., the content followed by Http:// can be and should be left behind; and thus, a browser will only interpret the rest of the URL as text.

(2) On page 22, line 11, "ELISA" should be spelled out in full for the first instance of use. See also page 77, line 8, "CD".

(3) For consistence, on page 77, line 18, "fig 10A" should be changed to "Fig. 10A".

(4) The Spec should make clarify the terms "OF1" (line 5 at page 78) and "KO" (line 12, page 78).

Objections to claims

(1) Claim 26 is objected to because the claim is written as an improper form of claim dependency, i.e., dependent from both claim 25 and 1, and because claim 26 is improperly depends from non-elected claim 1..

(2) In claim 28, "the ethanolamine is about 20mM ethanolamine" should be changed to "the concentration of ethanolamine is about 20 mM". Similarly, in claim 30, "the SB-12 is 0.2% SB-12" should be changed to "the concentration of the SB-12 is 0.2% (w/v or w/w)"; note that here, the "unit" for "0.2%" must be included.

(3) In claim 35, step *a*, line 3, before "optionally" the term "and" should be added.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. ə 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. ə 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

On page 5, line 29, the sequences of one peptide are disclosed without SEQ ID NO identification.

On page 14, lines 4, 19 and 28, the sequences of three peptides are disclosed without SEQ ID NO identification.

On page 15, lines 3, 11, 20 and 28, the sequences of four peptides are disclosed without SEQ ID NO identification.

On page 16, lines 30 and 31, the sequences of two peptides are disclosed without SEQ ID NO identification.

On page 79, lines 11, 14, 20 and 27, the sequences of four peptides are disclosed without SEQ ID NO identification.

On page 80, line 30 to page 81, line 25, the sequences of two peptides are disclosed without SEQ ID NO identification.

On page 83, line 51 to page 84, line 3, the sequence of one polypeptide is disclosed without SEQ ID NO identification.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. ə 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objection to drawings

Figures 5-6 are objected to because these figures should be labeled "prior art".

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is unclear as to whether or not "the FrpB protein", which is subjected to "refolding" by contacting it with the refolding buffer, is a (i) native or folded or (ii) partially folded/unfolded, or (iii) totally unfolded protein, (iv) a mutant thereof, or mixture of (i), (ii) , (iii) and (iv). The dependent claims 26-35 are also rejected.

Claims 30-31 should make clear that what is the concentration "unit" of "0.25". In the absence of clarification of this, the scope of the claims is ambiguous.

Claim 33 recites "further comprises guanidium chloride"; the recitation is awkward and vague because the term "further" renders the claim contrary to the limitation of claim 32 from which claim 33 depends becasue "further comprises" means that claim 32 must not contain "guanidium chloride"; yet, the limitation of claim 32 sets forth the refolding buffer contains "guanidium chloride" due to "and" before "urea". Does it refer to that the "refolding buffer" further comprises additional amount of guanidium chloride which is added secondarily?

Claim 35 recites steps *a*, *b* and *d* are "optional" while step *c* is not; and thus, claim 35 can be solely directed to one step, i.e., "step *c*". Step *c* recites "contacting the solubilised FrpB with the refolding buffer"; the recitation appears to lack antecedent basis for limitation "the solubilised", given that step *b* reciting "solubilization of …" is not required herein due to "optional" (a conditional language).

*Note that the specification does not define that "refolding" includes folding the protein from "the inclusion body" (step b of claim 35) comprising FrpB polypeptide; and claim 25 is directed to a method of refolding an FrpB" protein not a method of recombinant production thereof. Thus claim 35, which is directed to recombinant production of "FrpB" polypeptide/protein), has no basis in claim 25.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope enablement

Claims 25-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for a method of refolding FrpB protein comprising contacting said protein with working concentration of the refolding buffer containing Zwittergent 3-12, and properly refolded and isolated FrpB protein having bioactivity, does not reasonably provide enablement for (i) a method of refolding a FrpB protein including the deletion mutants thereof using undetermined non-working concentration of Zwittergent 3-12; and, (ii) a method of refolding deletion mutants of FrpB protein wherein the "deletion" (genus) encompasses deletions of more one amino acids up to truncation of unlimited peptide fragments of FrpB. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the

invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. Each factor applicable is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/(2) The nature of the invention:

Claim 25 as written is directed to refolding FrpB with any ranges of concentration of Zwittergent 3-12 in the refolding buffer, wherein said "nay range" refers to much lower or higher than working concentration of said buffer. Claim 26 and dependent claims therefrom are directed to a method of refolding an mutant FrpB protein; Claims 38 and dependent claims therefrom are directed to a pharmaceutical composition comprising the refolded "deletion mutants" of FrpB; wherein both claims 26 and 38 as written incorporates the structural limitation of claim 1 (non-elected, see above), i.e., "an FrpB protein having one or more deletions" (see claim 1).

The claims are broadly drawn to the "genus" (more one deletions in wild-type FrpB amino acid sequence) which encompasses unlimited truncations or/and deletions of amino acid residues 1-712 (see claim 26 incorporates claim1 limitation as to "*deletions*". Note that the full-length FrpB has 713 amino acids, see pages 83-84 of the Spec). Although the Spec teaches the loops of FrpB B polypeptide can be deleted, e.g., lops 5 and 7 (Examples 1-2 and [0023-0025]), the Spec fails to teach deletions of more one amino acids up to truncation of unlimited peptide fragments of FrpB. It is of note that the Spec does not define "non-conserved amino acids" of

FrpB; and thus, it is taken as "deletions of any amino acids" in FrpB sequence. The Spec fails to teach deletions of amino acid residues outside of the above-discussed loops can be refolded into bioactive conformation. The deletions would result in "non-FrpB" peptide/polypeptide, i.e., any proteins or enzymes having peptide (including oligopeptide) length generated by the deletion thereof, and result in unfolded (not refoldable) or partially folded proteins which are inactive. The art teaches that not all proteins are refoldable (see page 851, Figure 1 legend, Verbeke et al. (2001) *Cell Biol. Intern.*, 25, 845-857).

In addition, claim 25 does not set forth working concentration of Zwittergent 3-12 so as to allow the FrpB polypeptide to "refold". It has been reported that outside working concentration Zwittergent 3-12 ("z-3-12") does not mediate refolding of the denatured protein such as denatured rhodanase (see page 4488, Figure 1, Tandon et al. (1989) *J. Biol. Chem.*, 262, 4486-4491). This suggests that it is not feasible to use any concentration of zwitterionic detergent: Zwittergent 3-12 in the refolding buffer to refold the FrpB or/and deletion mutants thereof. Thus, the claimed invention is outside scope of enablement.

(3) The unpredictability of the art:

The relative art teaches that, in spite of extensive study over many years refolding of proteins (from inclusion bodies) is an unpredictable process that must be considered on a case by case basis (Liddell J. M. (2004) *SGM 154 Meeting abstracts*, 29 March-2 April 2004, University of Bath, page 22). Thus, level of the unpredictability of the art is high.

(4) The quantity of experimentation necessary:

The "deletions" will produce large amount of mutants; of them, some would have been unrefoldable, and require corresponding working concentration of the refolding chemical such as

Sb-12. Thus, screening for and characterizing these mutants for practicing the full scope of the claimed invention requires a large quantity of experimentation.

(5) The state of the prior art:

Although the Spec teaches characterization of the refolded products using circular dichroism (CD) spectroscopy (page 77), and although the art teaches use of PCR-assisted mutagenesis for unidirectional deletion (see [0160] of the Spec) and constructing expression vector for producing the deletion mutants, the experimentation to practice the full scope of the claimed invention, however, would not be routine to one skilled in the art. This is because different unfolded polypeptides/peptides have their "working concentration" of refolding agent, e.g., Zwittergent 3-12 (see the above Tandon et al. teachings) and the refolding condition should be determined in case by case (see abstract, Tandon et al.). Additionally, this is because each deletion mutants of FrpB polypeptide/peptide has its own folding or refolding pathway or profile which requires the skilled artisan to predetermine parameters (e.g., concentration of refolding agent") which are neither provided by instant Spec nor by the art in the relative field; or, many would be non-refoldable (see Verbeke et al.).

Furthermore, the relative art (page 25596, right column, lines 1-5, Christmas et al. (1999) *J. Biol. Chem.* 274, 25594-25598) teaches that, in general, the deletions may affect folding (or refolding) and disrupt the molecule over a more extensive region, which cannot be resolved by the routine experimentation. For instance, even single amino acid deletion, e.g., deletion of the C-terminal isoleucine, is sufficient to cause improper folding or refolding (see page 25596, right column). This indicates that experimentations of predicting, preparing deletion mutations and successfully producing refolded/bioactive mutant proteins are not routine.

(6) The relative skill of those in the art:

The level of skill in this art exceeds routine expatriation, and requires at least a molecular biologist with several years of experience in molecular cloning, bacteriology, biochemistry as well as knowledge in toxicology of bacterial pathogens and organic chemistry. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

* *Discussion of written description*

Claim 25 and dependent claims therefrom are directed to a method of refolding an FrpB protein which comprises one or more deletions of non-conserved amino acids. The Spec teaches that the deletions are in one or more of loops 1, 2, 4, 6, 8, 9, 10, 11, 12 and 13 (see paragraphs [0014-0016, and [0018-0022]; particularly, in loops 5 and 7 (see Examples 1-2 and [0023-0025]) as representative examples. Also, the Spec has provided factual indicia that the refolded deletion mutants of FrpB has biological activity compared to unfolded deletion mutants thereof (Table 78, page 78, Example 4) (see Examples 3 and 4), and described the concentration of SB-12 as refolding agent for the refolding thereof (see page 31 line 16 to page 34, line 15) Thus, the Spec has provided adequate written description and applicants are in possession of the claimed invention.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

- Claim 36 is rejected under 35 U.S.C. 102(b) as being anticipated by Ejima et al. (US Pat. No. 6084076).

At Example 3, table 3, Ejima et al. teach a refolding buffer comprising 0.4% SB-12, which anticipates claim 36.

Provisional Rejections -Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-31 and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9-15, 20 and 21 of Application No. 10525889 (**889**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claim 1-2 of 889 discloses a method of refolding an NspA protein comprising contacting the NspA with the refolding buffer containing Zwittergent 3-12, i.e., SB-12 compound, which is an obvious variation of instant claim 26-27. This is because claim 26 as written is broadly drawn to refolding a protein which is the "deletion" mutant (see above) structurally distinct/different from FrpB due to claim 26 incorporating the structural limitation (from "non-elected claim 1, see above "*Objection to claims*"): "one or more deletions"; and thus, "NspA" is considered to be structural variant of "FrpB" deletion mutant.

*Note that "non-conserved amino acids" which follows "... deletions" is considered to be any amino acids because instant Spec fails to teach what are the non-conserved amino acids of FrpB "compared to a corresponding wild-type FrpB protein" as recited in instant claim 1 from which instant claim 26 incorporates the structural limitation.

Claims 3, 4, 5 and 6 of 889 is identical to instant claims 28, 29, 30 and 31, respectively.

Claim 9 of 889 is obvious variation of instant claim 35.

Conclusion

No claims are allowed.

Discussion of art

The following art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

[1] Koprtekass et al. (*Thirteen International pathogenic Neisseria Conference* (2002, Sept. 1-60 Norwegian Institute of Public Heath, Oslo, Norway, page 126) teach in vitro refolding FrpB protein from inclusion bodies. This reference is not prior art because it does not antedate the instant claims.

[2] Koprtekass et al. (*Microbes Infection* (2006) 8, 2145-2153) teaches refolding of FrpB protein from the inclusion bodies wherein the protein is expressed and produced using SB-12 compound as refolding agent (page 2146). This reference is not prior art becasue it does not antedate the instant invention.

[3] Sparling et al. (US Pat. No. 6265567 B1) teach the isolated FrpB protein (col. 3, lines 25-61), and is derived from *N. meningitides* (see abstract). Becasue this reference does not teach refolding/folding method comprising contacting refolding agent SB-12 with FrpB polypeptide or variant thereof, this reference is not the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

/Samuel W Liu, Ph.D./
Examiner, Art Unit 1656
July 29, 2008

/Karen Cochrane Carlson, Ph.D./
Primary Examiner, Art Unit 1656